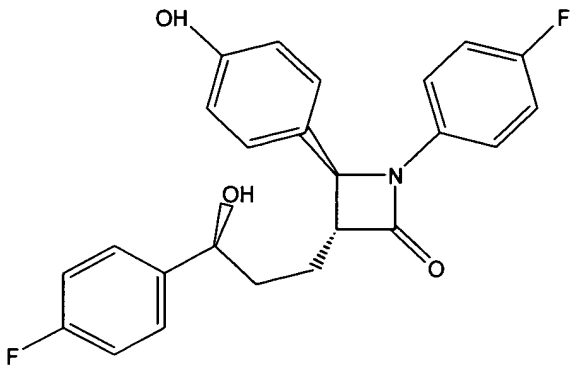
isomers, prodrugs, or pharmaceutically acceptable salts or solvates thereof (see original claim 2 for moiety definitions); and

(b) at least one blood modifier for vascular conditions which is different from component (a) above

(original claim 2 and page 15, line 23 - page 17, line 4 of the specification).

In the Office Action of August 27, 2003, Applicants were required to elect a species of sterol absorption inhibitor, blood modifier, and third therapeutic agent. Applicants provisionally elected with traverse ezetimibe, which is represented by Formula (II) below:



(II).

Ezetimibe is the active ingredient in ZETIA® pharmaceutical formulation, which is commercially available from MSP (Merck Schering-Plough) Pharmaceuticals, Inc. See Response to Restriction Requirement and Election of Species of September 9, 2003 ("Response").

In the same Response, Applicants provisionally elected with traverse aspirin as the blood modifier and simvastatin (an HMG CoA reductase inhibitor) as the third therapeutic agent.

The claimed compositions, combinations and treatment methods can be useful for treating vascular conditions and/or lowering concentration of a sterol in plasma in a mammal (page 72, lines 13-18 of the specification).

Applicants submit herewith for consideration the Declaration of Harry Davis, Jr., Ph.D. ("Davis Declaration"). Dr. Davis has a Bachelor of Science in Animal and Veterinary Science degree from the University of Maine (1977), Master of Science in Anatomical Pathology degree from George Washington University (1979) and a

Doctorate Degree in Pathology from the University of Chicago (1982) (Declaration at paragraphs 1-3).

Dr. Davis is employed by Schering-Plough Research Institute ("Schering") as a Distinguished Research Fellow in the field of Cardiovascular and Metabolic Disease and has been employed in this capacity since 1993 and was previously employed by Schering as a Principal Scientist since November 1987. (Declaration at paragraph 4). Dr. Davis' duties at Schering have included pharmaceutical drug discovery and basic research in lipid absorption and metabolism and metabolic disease. (Declaration at paragraph 5).

As discussed in Dr. Davis' Declaration, hypercholesterolemia has been associated with an increased sensitivity for platelets to aggregate and cause vascular complications. (Declaration at paragraph 6). A study was conducted under Dr. Davis' supervision to determine if a reduction in plasma cholesterol levels by ezetimibe (EZ) would enhance the ability of aspirin (ASA) to act as a platelet aggregation inhibitor. (Declaration at paragraph 6).

Rats were fed a 1% cholesterol + 0.5% cholate diet (HC) alone or containing ezetimibe (0.0036%, 3 mg/kg/day) for 7 days. (Declaration at paragraph 6). On day 7 they were treated with aspirin at 100 mg/kg or vehicle, and platelet aggregation determined. (Declaration at paragraph 6). Mean plasma cholesterol levels were reduced from 344 ± 22 mg/dl to 60 ± 4 mg/dl by ezetimibe treatment. (Declaration at paragraph 6). Platelet aggregation by adenosine diphosphate (ADP) and collagen was not altered, as expected, among the groups. (Declaration at paragraph 6). Arachidonic acid (AA) induced platelet aggregation at 0.3 mM was increased by the hypercholesterolemic diet compared to normal chow fed rats (Table), indicating an increased sensitivity to aggregate with hypercholesterolemia. (Declaration at paragraph 6). AA induced aggregation was not reduced in the aspirin alone treated hypercholesterolemic animals. (Declaration at paragraph 6). **AA induced aggregation was significantly reduced in the aspirin + ezetimibe treated rats compared to the aspirin alone treated hypercholesterolemic rats** (Table). (emphasis added) (Declaration at paragraph 6).

Table: Platelet Aggregation

Agonist	Regular Chow	High Cholesterol (HC) diet	HC + EZ	HC + ASA (100 mpk)	HC + EZ + ASA (100 mpk)
AA (0.3 mM)	7 ± 3	14 ± 2	13 ± 2	12 ± 2	7 ± 2
AA (1 mM)	16 ± 2	17 ± 3	16 ± 3	14 ± 2	5 ± 2
ADP (10 µM)	24 ±1	21 ± 2	21 ± 3	25 ± 2	31 ± 1
Collagen (3 µg/ml)	25 ± 1	24 ± 3	27 ± 3	30 ± 2	32 ± 1

Aggregation in whole blood (ohms)

N=6 per group, Mean ± SEM

In Dr. Davis' opinion, these results indicate that the combination of ezetimibe with aspirin enhances the ability of aspirin to inhibit platelet aggregation, and combination of ezetimibe and aspirin will prevent vascular complications greater than either agent alone. (Declaration at paragraph 6). *The above test data provide evidence of unexpected synergy of the combination of ezetimibe and aspirin to inhibit platelet aggregation when compared to treatment with aspirin alone or ezetimibe alone.*

The Rejection

At pages 3-5 of the Office Action, claims 1, 3, 11, 18-20, 35-37, 42-45 and 47 were rejected under 35 U.S.C. § 103(a) over EP 0720599 ("Rosenblum et al.") and WO 99/47123 ("Ullah") in view of Frei (Proc Soc Exp Biol Med. 1999 Dec; 222(3): 196-204).

In the Office Action, it is alleged that Rosenblum et al. disclose that compositions including the compound of Formula II can be combined with HMG CoA reductase inhibitors such as simvastatin to reduce cholesterol and risk of atherosclerosis (Final Office Action at page 3). Ullah teaches a composition comprising statins, such as

simvastatin, in combination with aspirin, for cholesterol lowering and treating or reducing the risk of developing atherosclerosis (Final Office Action at page 3).

It is acknowledged in the Final Office Action that the primary references do not expressly teach the claimed composition comprising the compound of Formula II (ezetimibe), aspirin and simvastatin together or that antioxidants be incorporated into such as composition (Final Office Action at page 3). It is alleged that Frei teaches that antioxidants such as vitamins C or E can be useful for inhibiting atherogenesis and normalizing vascular functions. (Final Office Action at page 4).

It is further alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the compound of Rosenblum et al. into Ullah, which are known to be useful to reduce cholesterol level and the risk of atherosclerosis individually, into a single composition useful for the very same purpose, citing *In re Kerkoven*, 205 U.S.P.Q. 1069 (Final Office Action at page 4). Further, it is argued that one of ordinary skill in the art would have been motivated to include an antioxidant since vitamin C, an antioxidant, is known to inhibit the development of atherosclerosis (Final Office Action at page 4).

The Prior Art

Rosenblum et al. disclose the compound of Formula II (ezetimibe) at page 29, Ex. 6. Rosenblum et al. disclose starch-based pharmaceutical compositions including compounds of Formula I of Rosenblum et al. (Ex. A and B Page 29). Rosenblum et al. teach that the active compounds therein can be combined with HMG CoA reductase inhibitors, such as simvastatin (Page 5, paragraph 0028). Rosenblum et al. also disclose that the active compounds are useful for reducing cholesterol and the risk of atherosclerosis (claims).

Ullah discloses the use of a combination of aspirin for reducing myocardial infarction and a statin (such as simvastatin) for lowering cholesterol and preventing or treating atherosclerosis at page 1, lines 14-18, in combination.

Frei discloses that antioxidants may inhibit atherogenesis and improve vascular function by two different mechanisms (Abstract). Lipid-soluble antioxidants present in LDL, such as vitamin C, can inhibit LDL oxidation (Abstract). Antioxidants present in

the cells of the vascular wall decrease cellular production and release of reactive oxygen species (ROS), inhibit endothelial activation and improve the biologic activity of ENDO (Abstract).

The Required Prima Facie Case of Obviousness Under 35 U.S.C. § 103 Has Not Been Established

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The Examiner can satisfy this burden only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious *unless the prior art suggests the desirability of the modification* (emphasis added). In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, **with due consideration to the persuasiveness of any arguments and any secondary evidence**." Manual of Patent Examining Procedure, (Rev. 1, Feb. 2003) § 716.01(d) (emphasis added) and In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

Claims 1, 3, 11, 18-20 and 47

Claims 1 and 47 recite a composition and therapeutic combination, respectively, comprising a sterol absorption inhibitor of Formula I shown above, isomers, prodrugs, or pharmaceutically acceptable salts or solvates thereof; and at least one blood modifier for vascular conditions which is different from the sterol absorption inhibitor.

Claim 3 depends from claim 1 and recites the compound of Formula II (ezetimibe) as the compound of Formula I.

Claim 11 depends from claim 1 and recites specific groups of blood modifiers. Claims 18-20 depend directly or indirectly from claim 1 and recite that the blood modifier is a platelet inhibitor, such as aspirin.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of sterol absorption inhibitor (such as that of Formula (I) (e.g., ezetimibe)) and blood modifier such as aspirin.

Applicants wish to emphasize that claim 1 does not require the presence of an optional third component, such as a statin.

With respect to patentability of a composition or combination of a sterol absorption inhibitor and blood modifier such as aspirin, Rosenblum does not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin. Rosenblum does not suggest or disclose that the disclosed sterol absorption inhibitors have any effect on platelet aggregation.

Ullah does not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin. Further, in Ullah, *aspirin is disclosed as being useful for reducing myocardial infarction* at page 1, lines 14-18, *not for treating atherosclerosis*. Ullah does not disclose sterol absorption inhibitors. The statin in Ullah is disclosed as lowering cholesterol and treating atherosclerosis. Id.

In the final Office Action at pages 4 and 5, *In re Kerkoven* was cited as supporting the argument that combining the compositions of Rosenblum and Ullah, which are known to be useful to reduce cholesterol level and the risk of atherosclerosis individually, into a single composition useful for the very same purpose would be considered obvious.

However, Ullah does *not* disclose aspirin as being useful for lowering cholesterol or treating atherosclerosis, but rather for treating myocardial infarction. Therefore *In re Kerkoven* does not apply since Ullah does not disclose aspirin as having the same purpose as a cholesterol absorption inhibitor or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis.

Frei does not disclose sterol absorption inhibitors or blood modifiers such as aspirin.

Even if the teachings of Frei were combined with those of Rosenblum et al. and Ullah as suggested in the Final Office Action, one skilled in the art would not be motivated to provide a composition having a sterol absorption inhibitor and blood modifier such as aspirin. *In re Kerkoven* does not apply since Ullah only discloses aspirin as useful for treating myocardial infarction and does not disclose aspirin as having the same purpose as a cholesterol absorption inhibitor or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis.

Further, Applicants respectfully request consideration of the evidence set forth in the Davis Declaration. These results indicate that the combination of ezetimibe with aspirin enhances the ability of aspirin to inhibit platelet aggregation, and combination of ezetimibe and aspirin will prevent vascular complications greater than either agent alone. (Declaration at paragraph 6). The above test data provide evidence of unexpected synergy of the combination of ezetimibe and aspirin to inhibit platelet aggregation when compared to treatment with aspirin alone or ezetimibe alone. None of the cited references, taken alone or combined as set forth in the rejection, suggests or discloses the unexpected synergy of the combination of ezetimibe and aspirin to inhibit platelet aggregation. Affidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103. M.P.E.P. 716.01(a). The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983) that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." M.P.E.P. 716.01(a). Applicants respectfully request that these unexpected results be considered as evidence of non-obviousness in the determination of patentability.

Therefore, the prima facie case of obviousness based upon Rosenblum et al., Ullah and Frei has not been established and the rejection of claims 1, 3, 11, 18-20 and 47 should be reconsidered and withdrawn.

If claim 1 is determined to be non-obvious, then all of the claims dependent upon claim 1 also should be determined to be non-obvious.

Claims 35-37

Claims 35-37 depend from claim 1 and further recite at least one HMG CoA reductase inhibitor, such as simvastatin. Thus the composition would comprise sterol absorption inhibitor, blood modifier such as aspirin, and HMG CoA reductase inhibitor, such as simvastatin.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of sterol absorption inhibitor (such as that of Formula (I) (e.g., ezetimibe)), blood modifier such as aspirin, and HMG CoA reductase inhibitor.

As discussed above, Rosenblum et al. and Ullah provide no motivation for a triple combination of sterol absorption inhibitor, blood modifier such as aspirin, and HMG CoA reductase inhibitor. *In re Kerkoven* does not apply since Ullah only discloses aspirin as useful for treating myocardial infarction and does not disclose aspirin as having the same purpose as a cholesterol absorption inhibitor or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis. Frei only discloses antioxidants as useful for treating atherosclerosis and therefore is not relevant to the rejection of these claims. Applicants respectfully request consideration of the evidence of unexpected results of the combination of ezetimibe and aspirin as set forth in the Davis Declaration and as discussed above as evidence of non-obviousness in the determination of patentability.

Therefore, the prima facie case of obviousness based upon Rosenblum et al., Ullah and Frei has not been established and the rejection of claims 35-37 should be reconsidered and withdrawn.

Claims 42-45

Claims 42-45 depend from claim 1 and further recite at least one antioxidant or vitamin. Thus the composition would comprise sterol absorption inhibitor, blood modifier such as aspirin, and antioxidant or vitamin.

Applicants wish to emphasize that claim 1 does not require the presence of a third component, such as a statin.

With respect to patentability of a composition or combination of a sterol absorption inhibitor, blood modifier such as aspirin and antioxidant or vitamin (*without the presence of a statin*), Rosenblum does not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin. Ullah does not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin.

In Ullah, *aspirin is disclosed as being useful for reducing myocardial infarction* at page 1, lines 14-18, *not for treating atherosclerosis*. The statin in Ullah is disclosed as lowering cholesterol and treating atherosclerosis. Id.

In the final Office Action at pages 4 and 5, *In re Kerkoven* was cited as supporting the argument that combining the compositions of Rosenblum and Ullah, which are known to be useful to reduce cholesterol level and the risk of atherosclerosis individually, into a single composition useful for the very same purpose would be considered obvious.

However, the invention of claims 42-45 is for a sterol absorption inhibitor, blood modifier such as aspirin and antioxidant or vitamin. Ullah does *not* disclose aspirin as being useful for lowering cholesterol or treating atherosclerosis. *In re Kerkoven* does not apply since Ullah only discloses aspirin as useful for treating myocardial infarction and does not disclose aspirin as having the same purpose as a cholesterol absorption inhibitor

or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis.

Frei does not disclose sterol absorption inhibitors or blood modifiers such as aspirin. Even if the teachings of Frei were combined with those of Rosenblum et al. and Ullah as suggested in the Final Office Action, one skilled in the art would not be motivated to provide a composition having a having a sterol absorption inhibitor, blood modifier such as aspirin and vitamin or antioxidant.

Applicants respectfully request consideration of the evidence of unexpected results of the combination of ezetimibe and aspirin as set forth in the Davis Declaration and as discussed above as evidence of non-obviousness in the determination of patentability.

Therefore, the prima facie case of obviousness based upon Rosenblum et al., Ullah and Frei has not been established and the rejection of claims 42-45 should be reconsidered and withdrawn.

Accordingly, Applicants respectfully request that the § 103(a) rejection of claims 1, 3, 11, 18-20, 35-37, 42-45 and 47 be reconsidered and withdrawn. Also, Applicants respectfully request rejoinder and allowance of the claims withdrawn by restriction, which were timely traversed.

Respectfully submitted,

Date: **November 3, 2005**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: T. Kosoglou et al.	:	Examiner: San-Ming R. Hui
Serial No.: 10/056,680	:	Group Art Unit: 1617
Filed: January 25, 2002	:	Atty. Docket No.: CV01492K
For: Combinations of Sterol Absorption Inhibitor(s) with Blood Modifiers for Treating Vascular Indications	:	

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF HARRY DAVIS, Jr., Ph.D.

I, Harry Davis, Jr., declare and state that:

1. I obtained a Bachelor of Science in Animal and Veterinary Science degree from the University of Maine in 1977.

2. I obtained a Master of Science in Anatomical Pathology degree from George Washington University in 1979.

3. I obtained a Doctorate Degree in Pathology from the University of Chicago in 1982.

4. I am employed by Schering-Plough Research Institute ("Schering") as a Distinguished Research Fellow in the field of Cardiovascular and Metabolic Disease and have

been employed in this capacity since 1993 and was previously employed by Schering as a Principal Scientist since November 1987.

5. My duties at Schering have included pharmaceutical drug discovery and basic research in lipid absorption and metabolism and metabolic disease.

6. Hypercholesterolemia has been associated with an increased sensitivity for platelets to aggregate and cause vascular complications. A study was conducted under my supervision to determine if a reduction in plasma cholesterol levels by ezetimibe (EZ) would enhance the ability of aspirin (ASA) to act as a platelet aggregation inhibitor. Rats were fed a 1% cholesterol + 0.5% cholate diet (HC) alone or containing ezetimibe (0.0036%, 3 mg/kg/day) for 7 days. On day 7 they were treated with aspirin at 100 mg/kg or vehicle, and platelet aggregation determined. Mean plasma cholesterol levels were reduced from 344 ± 22 mg/dl to 60 ± 4 mg/dl by ezetimibe treatment. Platelet aggregation by adenosine diphosphate (ADP) and collagen was not altered, as expected, among the groups. Arachidonic acid (AA) induced platelet aggregation at 0.3 mM was increased by the hypercholesterolemic diet compared to normal chow fed rats (Table), indicating an increased sensitivity to aggregate with hypercholesterolemia. AA induced aggregation was not reduced in the aspirin alone treated hypercholesterolemic animals. AA induced aggregation was significantly reduced in the aspirin + ezetimibe treated rats compared to the aspirin alone treated hypercholesterolemic rats (Table).

Table: Platelet Aggregation

Agonist	Regular Chow	High Cholesterol (HC) diet	HC + EZ	HC + ASA (100 mpk)	HC + EZ + ASA (100 mpk)
AA (0.3 mM)	7 ± 3	14 ± 2	13 ± 2	12 ± 2	7 ± 2
AA (1 mM)	16 ± 2	17 ± 3	16 ± 3	14 ± 2	5 ± 2
ADP (10 μM)	24 ±1	21 ± 2	21 ± 3	25 ± 2	31 ± 1
Collagen (3 μg/ml)	25 ± 1	24 ± 3	27 ± 3	30 ± 2	32 ± 1

Aggregation in whole blood (ohms)

N=6 per group, Mean ± SEM

In my opinion, these results indicate that the combination of ezetimibe with aspirin enhances the ability of aspirin to inhibit platelet aggregation, and combination of ezetimibe and aspirin will prevent vascular complications greater than either agent alone.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that those statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Nov 2, 2005

HARRY DAVIS, Jr., Ph.D.